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Reference Ranges for Fetal Atrioventricular and Ventriculoatrial Time Intervals and Their Ratios during Normal Pregnancy

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Keywords
Fetal heart rate · Fetal echocardiography · Prenatal diagnosis · Atrioventricular time · Ventriculoatrial time

Abstract
Background: The diagnostic assessment of fetal arrhythmias relies on the measurements of atrioventricular (AV) and ventriculoatrial (VA) time intervals. Pulsed Doppler over in- and outflow of the left ventricle and tissue Doppler imaging are well-described methods, while Doppler measurements between the left brachiocephalic vein and the aortic arch are less investigated. The aim of this study was to compare these methods of measurement, to find influencing factors on AV and VA times and their ratio, and to create reference ranges. ***Methods:*** Echocardiography was performed between 16 and 40 weeks of gestation in normal singleton pregnancies. Nomograms for the individual measurements were created using quantile regression with Matlab Data Analytics. Statistical analyses were performed with GraphPad version 5.0 for Windows. ***Results:*** A total of 329 pregnant women were enrolled. A significant correlation exists between AV and VA times and gestational age (GA) ($p = 0.0104$ to <0.0001, $\sigma = 0.1412$ to 0.3632). No correlation was found between the AV:VA ratio and GA ($p = 0.08$ to 0.60). All measurements differed significantly amongst the studied methods ($p < 0.0001$). ***Conclusions:*** AV and VA intervals increase proportionally with GA; no other independent influencing factors could be identified. As significant differences exist between the three methods of assessment, it is crucial to use appropriate reference ranges to diagnose pathologies.

Introduction

Fetal cardiac rhythm disturbances occur in about 2% of all pregnancies and account for 10–20% of all referrals to a fetal cardiologist [1]. While fetal electrocardiography (ECG) monitoring is difficult and not routinely obtainable in most centres, different methods of Doppler assessment of the fetal heart and adjacent vessels provide helpful alternatives in the differential diagnosis of fetal arrhythmias today. M-mode and tissue Doppler imaging (TDI) enable the recording of the sequence and time relationship of atrial and ventricular systolic wall movement during a heart cycle [2]. The simultaneous recording of blood flow by pulsed Doppler sonography of adja-

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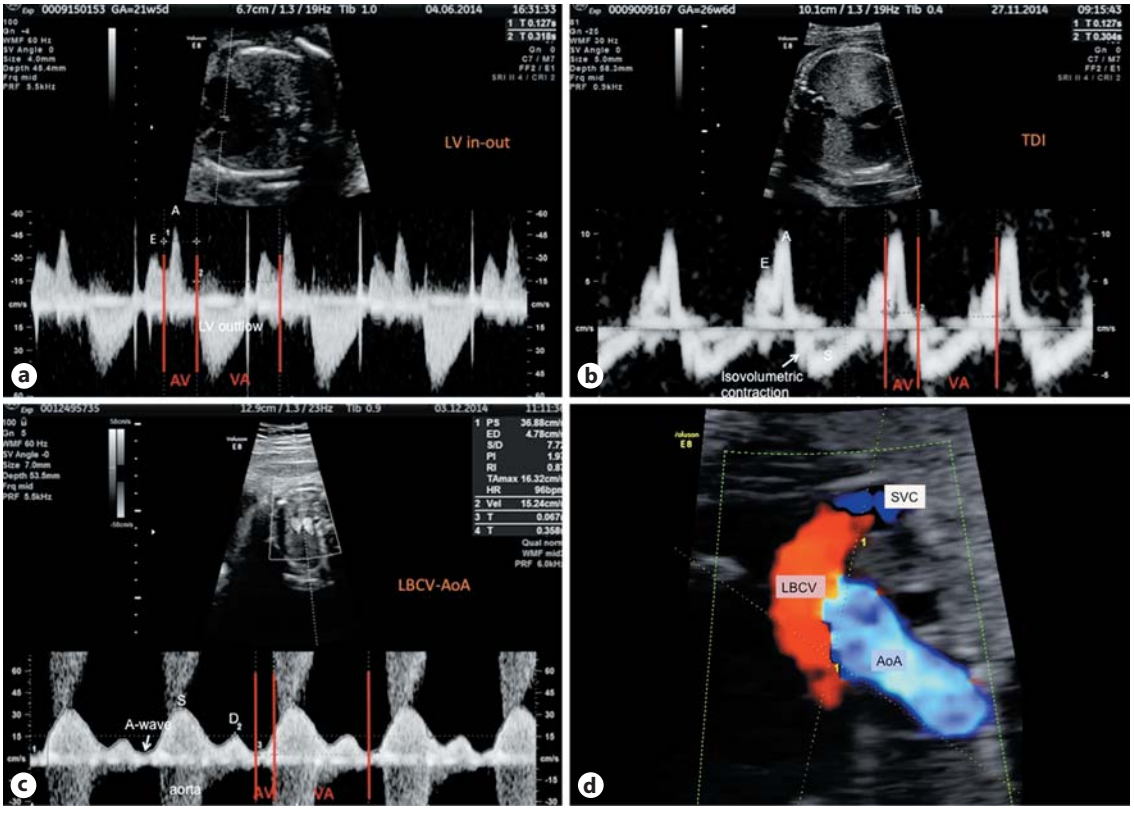

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Fig. 1. Illustration of the methods of measurement. **a** LV in-out: AV time is measured from the beginning of the active contraction of the atrium (E) to the beginning of the LV outflow, VA time vice versa. **b** TDI: AV time is measured from the E-wave of the atrial wall movement to the ventricular contraction movement (S), VA time vice versa. **c** LBCV-AoA: AV time is measured from the nadir of the A-wave to the aortic outflow, VA time vice versa. **d** Illustration of the intersection of the LBCV with the AoA. AoA, aortic arch; AV, atrioventricular; LBCV, left brachiocephalic vein; LBCV-AoA, intersection of the left brachiocephalic vein and the aortic arch; LV in-out, left ventricular in- and outflow; SVC, superior vena cava; TDI, tissue Doppler imaging; VA, ventriculoatrial.

cent arteries and veins follows the same concept [3–6]. With those different methods the mechanical atrioventricular (AV) time interval is assessed, which correlates with the electrical PR time on routine ECG [4].

Assessing the AV time is helpful in the differential diagnosis of bradycardia, in particular in diagnosing first-degree atrioventricular blocks (AVBs) [7], and in the differentiation of blocked supraventricular premature beats (premature atrial contractions) from second-degree AVBs [8]. The ventriculoatrial (VA) time, which corresponds to the RP interval on ECG, helps to distinguish re-entry tachycardia from sinus tachycardia, ectopic atrial tachycardia, and permanent junctional reciprocating tachycardia [8].

Measurements of AV times with pulsed Doppler over the left ventricular in- and outflow (LV in-out) tract, investigations of blood flow simultaneously over adjacent pairs of arteries and veins such as the ascending aorta and the superior vena cava (SVC) or over the renal artery and vein [9], and TDI-based assessment are well described in the literature. There is however little information available on the assessment of AV or VA times measured at the level of the left brachiocephalic vein (LBCV) and aortic arch (AoA), but also generally on VA times and their relations to AV intervals. The LBCV can be investigated at little or no angle of insonation throughout pregnancy, and the intersection with the AoA is found without difficulties in most cases.

The aim of this study was to create reference ranges for AV, but also for VA times and their ratio, comparing the three described methods and to gain insight into the relationship of AV and VA times throughout gestation.

Material and Methods

In consecutive pregnant women the fetal AV and VA times were measured during routine examination using three different methods: (1) pulsed Doppler over the LV in-out tract, (2) TDI over the tricuspid annulus, and (3) pulsed Doppler at the level of the intersection of the LBCV and the AoA (LBCV-AoA) (Fig. 1). All Doppler investigations were performed during fetal quiescence and apnoea on Voluson GE E8 and E10 machines (GE Healthcare Inc.), equipped with GE RM6C 3D/4D probes. The high-pass filter was set at 60 Hz and to a minimum for TDI, respectively. For all measurements 3–6 heart cycles were recorded. Inclusion criteria were singleton pregnancies with structurally normal fetuses between 16 and 40 weeks of gestation. Exclusion criteria were fetal growth restrictions defined as estimated fetal weight (EFW) below the 5th percentile, any known genetic abnormality, amniotic fluid abnormalities, and all cases with fetal arrhythmia or fetal anaemia. All patients with positive SSA and SSB antibodies or women with overt preeclampsia were also excluded. In case of serial measurements only the first available one was used for further analysis. All measurements were obtained by two certified sonographers only.

For the LV in-out measurement, we obtained an apical 4-chamber view of the heart and used pulsed Doppler with the gate set in the LV close to the crux of the heart to simultaneously assess the blood flow through the mitral and aortic valve. AV intervals were measured from the onset of the mitral A-wave (atrial systole) between the E- and A-peak to the beginning of the ventricular systole in the aortic outflow tract. Similarly, the VA intervals were measured from the ventricular to the atrial systole (Fig. 1a).

For TDI, the sample gate was placed over the lateral tricuspid valve annulus. The AV time was again measured between the A- and E-peak of the wall movement to the beginning of the ventricular contraction marked by negative movement of the tricuspid annulus, a method described by Nii et al. [7] as Aa-Sa measurement (atrial contraction to ventricular systole); the VA time was measured vice versa (Fig. 1b).

For the measurement performed at the level of the LBCV and the AoA, the sample gate was placed at the intersection of the LBCV and the AoA (Fig. 1d). As the A-wave is mostly positive, the beginning of the atrial contraction is not well defined, so we decided to assess the AV time from the nadir of the A-wave to the beginning of the ventricular contraction; again the VA time was measured vice versa (Fig. 1c).

Statistical analyses were performed with GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, CA, USA) and Matlab Data Analytics (MathWorks) for quantile regression. Linear regression analysis was used to evaluate the effect of gestational age (GA) on AV and VA times. Correlations were searched using the Spearman rank test. Mann-Whitney test, *t* test, and one-way ANOVA were used to compare continuous variables. Statistical significance was considered achieved when p was <0.05.

Reference ranges for AV, VA, and their ratio assessed by the various methods were constructed by quantile regression [10, 11]. The α% quantile curve is modeled as a polynomial of degree k for $k = 1,2,3$, which will be denoted by

$$p_{\alpha,k}(t) = c_{\alpha,k}t^k + \ldots + c_{\alpha,1}t + c_{\alpha,0},$$

where the coefficients c_i are estimated by quantile regression. The optimal value for the degree of the polynomial k is chosen by 10-fold crossvalidation [12].

Table 1. Maternal and fetal characteristics and pregnancy outcomes

Clinical characteristics	Median [IQR] or %
Median maternal age, years	32.6 [28.9–36.3]
Median maternal BMI at 12 weeks	22.5 [20.0–25.4]
Median GA at inclusion, weeks	27.7 [21.6–32.0]
Median estimated fetal weight	
Absolute, kg	1.10 [0.45–1.84]
Percentile	36.0 [19.0–59.0]
Fetal heart rate at inclusion, bpm	142 [137–148]
Nulliparous	38.9%
Cigarette smoker	8.8%
Chronic hypertension	2.7%
Pregestational diabetes mellitus	1.0%
SLE/SS/APS (SSA/SSB negative)	2.1%
Median GA at delivery, weeks	39.3 [38.2–40.4]
Median birth weight, kg	3.28 [2.79–3.54]
Median birth weight percentile	37.5 [17.6–60.0]

APS, antiphospholipid antibody syndrome; GA, gestational age; SLE, systemic lupus erythematosus; SS, Sjögren syndrome.

This study was approved by the Ethics Committee of the University of Bern (Basec No. 2016-00415).

Inter- and intraobserver variability were assessed by intraclass correlation coefficients (ICCs) calculated with SPSS 21 (IBM SPSS Statistics for Windows, Version 21; IBM Corp., Armonk, NY, USA). Agreement was considered slight with an ICC ≤0.2, fair with 0.2 < ICC ≤ 0.4, moderate with 0.4 < ICC ≤ 0.6, substantial with 0.6 < ICC ≤ 0.8, and almost perfect with ICC >0.8.

Results

During the study period we included 329 pregnancies with a complete assessment of all three methods of AV and VA time measurements. Maternal history and clinical characteristics as well as pregnancy outcomes are depicted in Table 1.

The median [IQR] AV and VA times for all methods are depicted in Table 2. A significant correlation was found between GA and all performed cardiac interval measurements (Table 2). Reference ranges were constructed, as explained, using quantile regression modeling. For each Doppler method the 5th, 10th, 50th, 90th, and 95th percentile for GA was calculated (Fig. 2) using the following equation:

$$p_{\alpha,2}(t) = c_{\alpha,2}t^2 + c_{\alpha,1}t + c_{\alpha,0}.$$

The coefficients (c) are listed in Table 3; α stands for the percentiles 5, 50, and 95, t stands for GA.

There was no correlation between AV or VA times and maternal characteristics; a correlation of the parameters existed with EFW ($p = 0.006$ to <0.0001, $r = 0.16$ to 0.32), but not with the percentiles of the EFW. There was also a negative correlation of all time intervals with fetal heart rate (FHR) ($p = 0.003$ to <0.0001, $r = -0.16$ to -0.73), but as the length of a heart cycle is the sum of the respective AV and VA times, FHR is not an independent parameter either.

The AV:VA ratio was GA independent by all three methods ($p = 0.08$ by LV in-out, $p = 0.55$ by LBCV-AoA, and $p = 0.60$ by TDI). Therefore, we can conclude that a proportional prolongation of AV and VA times exists throughout gestation (Fig. 2c, f, i). The median [IQR] AV:VA ratio was 0.19 [0.15–0.23] by LBCV-AoA, 0.40 [0.37–0.44] by LV in-out, and 0.44 [0.38–0.49] by TDI.

Table 2. Median [IQR] AV and VA time measurements by LBCV-AoA, LV in-out, and TDI and their correlations with GA

	Median [IQR], ms	Correlation with GA
AV time LBCV-AoA	67 [57–80]	$p = 0.0104$; $\sigma = 0.1412$
AV time LV in-out	122 [112–130]	$p = 0.0025$; $\sigma = 0.1660$
AV time TDI	129 [118–140]	$p < 0.0001$; $\sigma = 0.2539$
VA time LBCV-AoA	356 [337–378]	$p < 0.0001$; $\sigma = 0.3132$
VA time LV in-out	298 [283–317]	$p < 0.0001$; $\sigma = 0.3632$
VA time TDI	293 [277–311]	$p < 0.0001$; $\sigma = 0.3242$

The Spearman rank test was used to calculate correlations. AV, atrioventricular; GA, gestational age; LBCV-AoA, intersection of the left brachiocephalic vein and the aortic arch; LV in-out, left ventricular in- and outflow; TDI, tissue Doppler imaging; VA, ventriculoatrial.

When comparing the different ways of measurement, AV time, VA time, as well as AV:VA ratio were significantly different between the three groups ($p < 0.0001$) (Fig. 3).

Intra- and interobserver variability were assessed for all measurements obtained in a series of 20 fetuses. In all measurements ICCs were found to be >0.9, the only exception being the AV interval assessed by LV in-out, which performed slightly poorer. All results are depicted in Table 4.

Discussion

Our study demonstrates that AV and VA times are correlated with GA, EFW, and FHR, with GA as the only independent variable. AV and VA times increase proportionally, which results in a GA-independent AV:VA ratio. Both intervals as well as the ratio vary markedly with the Doppler method used. A high intra- and interobserver reliability was found for all measurements. It is therefore important to use appropriate reference ranges in the differential diagnosis of fetal arrhythmias.

Our results are in line with previously studies demonstrating a GA dependency of AV times. While Glickstein et al. [13] first did not demonstrate a correlation of AV times with GA, others found a linear correlation of AV times with GA and FHR as well as that GA is the only independent variable [6, 7]. Unlike in those studies, our data collected in a significantly larger cohort are not correlated linearly, but are better described by a second-order polynomial correlation to GA. To the best of our knowledge, this is the first study to have calculated reference ranges for VA times and AV:VA ratios as well.

Table 3. Polynomial coefficients (c) to solve the quantile regression equation

	$c_{5,2}$	$c_{5,1}$	$c_{5,0}$	$c_{50,2}$	$c_{50,1}$	$c_{50,0}$	$c_{95,2}$	$c_{95,1}$	$c_{95,0}$
Coefficients for AV times									
LBCV-AoA	0	0.512	34.361	0	0.485	53.954	0	0	93.000
LV in-out	–0.031	1.748	77.680	–0.021	1.373	100.185	–0.022	2.020	103.304
TDI	–0.036	2.205	68.470	–0.098	6.016	411.029	–0.108	7.395	38.266
Coefficients for VA times									
LBCV-AoA	0.001	–0.143	309.555	0.040	–0.573	341.415	0.133	–3.514	407.329
LV in-out	0	–0.215	266.551	0	1.708	253.204	0	3.329	251.972
TDI	0	0.896	232.012	0	1.434	256.949	0	2.921	262.246

α stands for the percentiles 5, 50, and 95. AV, atrioventricular; LBCV-AoA, intersection of the left brachiocephalic vein and the aortic arch; LV in-out, left ventricular in- and outflow; TDI, tissue Doppler imaging; VA, ventriculoatrial.

The first intrauterine assessment of AV and VA times to diagnose fetal rhythm disturbances dates back nearly 20 years and was initially attempted by M-mode echocardiography [14] and shortly thereafter also by pulsed Doppler sonography [2]. Already these first studies demonstrated that the measured times depend on the method they were assessed with [2]. Nii et al. [7] compared different ways of measuring AV time with fetal ECG. They concluded that TDI measurements between the atrial contraction and isovolumetric contraction (Aa-IV) correlated better with the ECG than TDI measurement between atrial and ventricular contraction (Aa-Sa) or LV in-out measurements. Furthermore, they found that measurements between the SVC and the aorta ascendens (SVC-Ao) exhibit the least correlation with ECG [7]. While the Aa-IV measurement underestimated the PR interval,

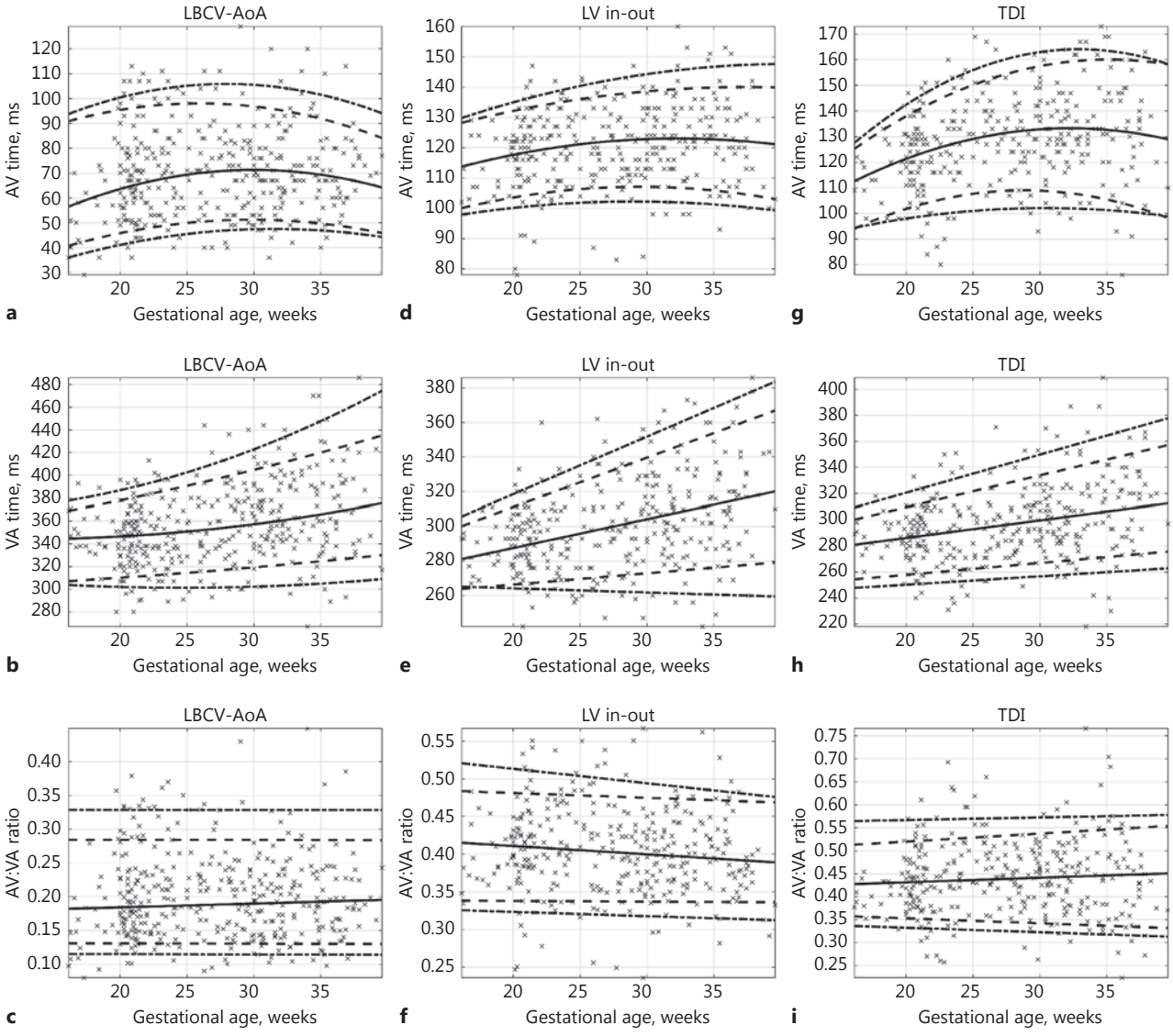

Fig. 2. Reference ranges for AV times, VA times, and AV:VA ratios between 16 and 40 weeks of gestation assessed by LBCV-AoA, LV in-out, and TDI. AV, atrioventricular; LBCV-AoA, intersection of the left brachiocephalic vein and the aortic arch; LV in-out, left ventricular in- and outflow; TDI, tissue Doppler imaging; VA, ventriculoatrial.

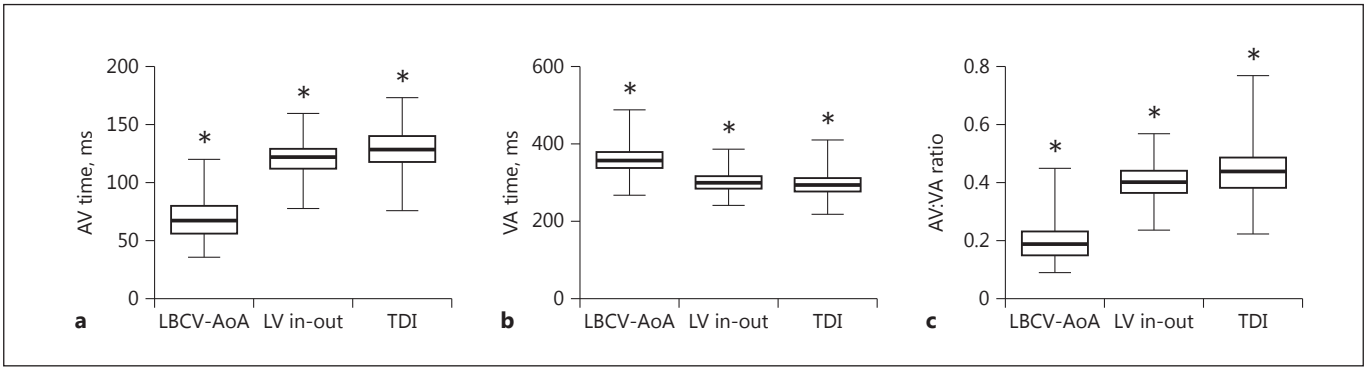

Fig. 3. AV and VA times as well as AV:VA ratios are significantly different by all three methods of assessment ($p < 0.01$). AV, atrioventricular; LBCV-AoA, intersection of the left brachiocephalic vein and the aortic arch; LV in-out, left ventricular in- and outflow; TDI, tissue Doppler imaging; VA, ventriculoatrial.

Table 4. Intraclass correlation coefficients of intra- and interobserver variability of each method of AV and VA time interval measurement and their 95% confidence intervals

	Intraobserver variability		Interobserver variability
	observer 1	observer 2	
AV time			
LBCV-AoA	0.95 (0.88–0.98)	0.90 (0.78–0.97)	0.95 (0.86–0.99)
LV in-out	0.85 (0.70–0.94)	0.75 (0.54–0.89)	0.88 (0.40–0.96)
TDI	0.94 (0.88–0.98)	0.90 (0.80–0.96)	0.94 (0.84–0.98)
VA time			
LBCV-AoA	0.96 (0.91–0.99)	0.96 (0.90–0.99)	0.98 (0.95–0.96)
LV in-out	0.98 (0.96–0.99)	0.91 (0.81–0.96)	0.97 (0.89–0.99)
TDI	0.97 (0.93–0.99)	0.95 (0.89–0.98)	0.97 (0.92–0.99)

AV, atrioventricular; LBCV-AoA, intersection of the left brachiocephalic vein and the aortic arch; LV in-out, left ventricular in- and outflow; TDI, tissue Doppler imaging; VA, ventriculoatrial.

they noticed an over-estimation by all other methods. In PD-derived measurements this is most likely explained by the fact that the time delay from the Q-wave to the ventricular ejection is longer than the delay from the P-wave to the atrial ejection [15]. Interestingly, at the same time a study in newborns also showed a highly significant positive correlation between AV times and PR intervals, and also a systematic over-estimation of the PR interval when measured by SVC-Ao and even more by LV in-out [16]. So, our findings of significantly different results for all three methods are in line with previously published data; however, in our collective the difference between TDI and PD was less evident than that described by Nii et al. [7]. AV times measured by LBCV-AoA, on the other hand, were shorter than by any other described method. This is due to the fact that in the LBCV, the A-wave is negative only in about 20% of all measurement (unpublished results), and therefore not the beginning, but the nadir of the A-wave was used for measurement (Fig. 1c).

In the diagnosis of a first-degree AVB, an AV time ≥150 ms by PD LV in-out was defined in the PRIDE study [17]. The critical time period for SSA and/or SSB antibodies to cause AVBs is between 18 and 24 weeks of gestation [16]. It remains a matter of debate whether first-degree AVBs can be accurately diagnosed prenatally and also if they do progress to higher degree AVBs and whether they should be treated [18, 19]. Our results show that with LV in-out the 99th percentile reaches 150 ms at

28.3 weeks of gestation while the 95th percentile never crosses 150 ms. However, as AV times measured by TDI are longer, using this method the 95th percentile is above 150 ms already after 22.5 weeks; therefore, applying the proposed cut-off would lead to over-diagnosis and eventually over-treatment of many fetuses at risk. Considering the controversies of high-dose intrauterine but also maternal steroid exposure, this distinction is even more crucial. AV times measured by LBCV-AoA, on the other hand, are significantly shorter and far from 150 ms in the normal population throughout gestation. As measurement inaccuracies are more important the shorter the actual measured time is, we believe that the diagnosis of a first-degree AVB should rely on LV in-out, TDI, or similar methods first.

The differential diagnosis of supraventricular fetal tachyarrhythmias is primarily based on the VA interval being shorter or longer than the AV interval [8]. Our results demonstrate that under physiological conditions, the VA time is about 2–5 times longer that the corresponding AV time. Re-entry tachycardias typically present with a VA time that is shorter than the AV time because a fast conducting accessory connection directs the electrical impulse from the ventricle back to the atria, and the AV:VA ratio will therefore increase to >1.0 [20]. While all other supraventricular fetal tachyarrhythmias are summarised as long VA tachyarrhythmias, it will be interesting in further studies to see whether the AV:VA ratio varies according to the underlying pathology, and to test the use of our reference ranges in that setting. The FHR decreases throughout gestation, a process that continues in infancy and has mostly been explained by the increasing dominance of the parasympathetic nervous system on the heart rate as pregnancy progresses [21]. As there is not only a gradual prolongation of the AV but also a proportional prolongation of the VA time, the whole cardiac cycle expands symmetrically.

In distinguishing premature atrial contractions from second-degree AVBs, using arterial and venous vessel pairs is helpful since the premature beat can very easily be detected as a reversed venous flow. While SVC-Ao measurements were proposed as the method of choice [22], the LBCV, thanks to its transverse course through the fetal thorax, can be found and assessed easily throughout gestation.

Recently, Rodriguez et al. [23] demonstrated that the AV interval is also prolonged in pregnancies diagnosed with intrahepatic cholestasis of pregnancy (ICP). At 36.7 weeks of gestation they found an AV interval of 121.4 ± 10 ms in the control group, which corresponds almost exactly to the 50th percentile of our measurements, while the AV interval in ICP was more than 10 ms longer on average, but still within the normal range according to our data. Eventually the finding of an longer AV interval in ICP patients might be helpful to time delivery in affected pregnancies, and we believe it would be interesting to see whether there is a correlation between AV intervals and bile acid levels, which are usually increased in ICP.

In conclusion, we have created reference ranges for AV, VA times, and AV:VA ratios using three different methods of measuring those factors, two more commonly used and one less investigated method. The study demonstrates that a fixed cut-off independent of GA and method of measurement cannot be useful in diagnosing first-degree AVBs. The same is likely to be true in the differential diagnosis of fetal tachyarrhythmias. Last, our routine use of the LBCV-AoA method proved to be easy, and we believe it will be helpful in differentiating bigeminal premature atrial contractions from second-degree AVBs.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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